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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,509	12/05/2003	Hong Zhang	ISPH-0803	9823

55389 7590 03/05/2007

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
ZARA, JANE J.	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,509	ZHANG ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-31-05, 12-5-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 12-12-06.

Claims 1-9 and 11-14 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1-9 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 9-18-06.

The claims are drawn to compositions and methods comprising the administration of compounds that are 8-50 nucleobases in length and specifically hybridize with the 3'UTR of SEQ ID NO: 17, which encodes BCL2-associated X protein (BAX). The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising these compounds that specifically hybridize with the 3'-UTR of SEQ ID NO> 17. The specification discloses antisense oligonucleotides that are 20 nucleotides in length and fully complementary to SEQ ID NO: 17. The specification does not disclose

any other sequences, including any sequences with less than 100% identity to the complement of SEQ ID NO: 17, that specifically hybridize with the 3'-UTR of SEQ ID NO. 17.

Applicant's arguments filed 12-12-06 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the genus of oligonucleotides claimed. Applicant also argues that Applicant need not provide each and every sequence to provide adequate description and that it requires routine experimentation to design such sequences. Additionally Applicant argues that the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Contrary to Applicant's assertions, the description of the target sequence and the disclosure of a number of antisense sequences that are fully complementary complementary and which provide for expression of target gene inhibition are not representative of the broad genus embracing any antisense oligonucleotide that specifically hybridizes to the 3'-UTR of SEQ ID NO. 17. Applicant is correct that undue experimentation is not required to design and assess the ability of oligonucleotides to inhibit the expression of a target gene in vitro, but the instant rejection is not for lacking enablement, but for lacking adequate written description. No species have been provided which have less than 100% identity with the target gene. The 20mer antisense oligonucleotides which are fully complementary to the target gene are not representative of the very broad genus claimed, which encompasses thousands of sequences. Written description is satisfied when a representative number of species, concisely describing the characteristics of the

members of the genus claimed, is provided at the time of filing. The question is not whether one of skill in the art could eventually identify the members of the genus claimed at some time in the future. For these reasons, the instant rejection for lacking adequate written description is maintained.

No common structural attributes identify the members of the claimed genus, and distinguish members within the claimed genus from those outside of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed, compounds that specifically hybridize with the 3'-UTR of SEQ ID NO. 17, encoding BAX. Thus, Applicant was not in possession of the claimed genus.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Korsmeyer, Dibbert et al and Manfredini et al, the combination in view of Milner et al and McKay insofar as the claims are drawn to compositions and methods of inhibiting the expression of SEQ ID No. 17, encoding the BCL2-associated x protein in vitro

comprising administration of a composition comprising an antisense oligonucleotide between 8-50 nucleobases in length that specifically hybridizes with the 3'-UTR of SEQ ID NO. 17, and inhibits the expression of SEQ ID NO: 17 in vitro, which oligonucleotide comprises a phosphorothioate internucleotide linkage, a 2'-O-methoxyethyl sugar moiety and a 5'methyl-cytosine, and which is optionally a chimeric oligonucleotide, and which composition further comprises a colloidal dispersion system.

Korsmeyer (6,500,626) teach the in vitro inhibition of expression of SEQ ID No. 17, encoding the BCL2-associated x (BAX) protein, using antisense oligonucleotides (see col. 29 and col. 46, lines 54-56).

Dibbert et al (Proc. Natl. Acad. Sci., Vol. 96, No. 23, pages 13,330-13,335) teach the inhibition of human BAX expression in vitro using antisense oligonucleotides to study the role of BAX in apoptosis (see the abstract on p. 13,330; fig. 4 on p. 13,334; fig. 5 and table 2 on p. 13,333).

Manfredini et al (Antisense & Nucleic Acid Drug Dev., Vol. 8, pages 341-350, 1998) teach the inhibition of expression of human BAX (Seq ID No. 17) using antisense oligonucleotides in order to study the role of BAX in the regulation of apoptosis (see the abstract and introduction on pp. 341-342; table 1 on p. 342; bridging paragraph on pp. 343-344, fig. 1 on p. 344; figs. 2 and 3 on p. 345; fig. 6 on p. 347).

The primary references of Korsmeyer, Dibbert and Manfredini do not teach the inhibition of BAX expression using antisense that specifically target the 3'-UTR of SEQ ID NO. 17, nor the administration of compositions to cells in vitro, nor the incorporation

of phosphorothioate internucleotide, 5-methyl cytosine or 2'-O-methoxytethyl sugar modifications into oligonucleotides, including chimeric oligonucleotides.

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro, including in the 5', 3' and stop codon regions of the target gene (See figure 1 on p 538 and figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach the administration to cells in vitro of colloidal dispersion compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which antisense target the various regions of recombinant nucleic acid, including the 3' UTR region of a target gene. McKay et al also teach the in vitro inhibition and screening of modulators (*e.g.* of various antisense oligonucleotides between 8-80 nucleobases that specifically hybridize with the target gene).

It would have been obvious to one of ordinary skill in the art to design and use antisense oligonucleotides between 8-50 nucleobases to target BAX encoded by SEQ ID NO. 17 because the sequence encoding human BAX was well known in the art as taught previously by Korsmeyer. Furthermore, the use of antisense to target and inhibit the expression of human BAX was routine in the art as evidenced by the teachings of

Dibbert and Manfredini. One of ordinary skill in the art would have been motivated to target the various regions of a nucleic acid encoding a target gene of interest, including the 5'UTR, the coding region and the 3'-UTR of a target gene because McKay, Milner and other have routinely targeted these regions of a target gene of interest with antisense for inhibition of expression and there was a reasonable expectation of success that antisense targeting these regions would inhibit target gene expression in vitro.

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein (BAX) in vitro, because Milner et al and McKay teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro, including the 3' UTR region of the target gene of interest, using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15). It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein in vitro comprising the administration of antisense oligonucleotides between 8-50 nucleobases because Milner teaches methods of designing and assessing antisense oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro, and Korsmeyer teach the nucleic acid sequence encoding human BAX and Dibbert, Manfredini and Korsmeyer teach the inhibition of expression of BAX in vitro using antisense oligonucleotides between 8-50 nucleobases in length. One of ordinary skill in

the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 8-50 nucleobases which best target and inhibit BCL2-associated x protein expression in order to study this target molecule's role in apoptosis, as taught previously by many others in the art, including Korsmeyer, Dibbert et al and Manfredini.

One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 8-50 nucleobases) for the in vitro inhibition of BCL2-associated x protein expression. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have expected that the delivery of modified antisense oligonucleotides to target cells harboring BCL2-associated x protein, which antisense specifically hybridize with the target nucleic acid encoding BCL2-associated x protein (e.g. of the 3' UTR of SEQ ID No. 17), would lead to inhibition of expression of BCL2-associated x protein in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-15-07

JZara TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER